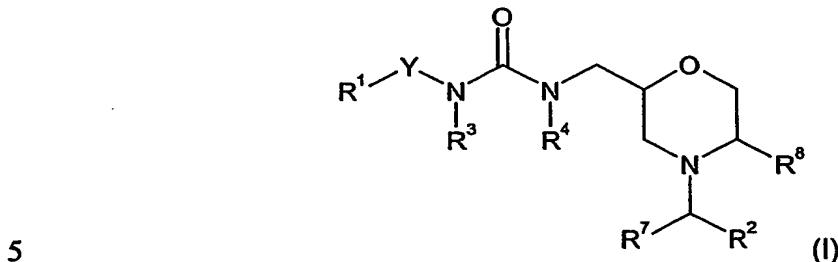


Claims

1. A compound of formula (I):



wherein:

- R^1 represents substituted or unsubstituted heteroaryl;
- Y represents $-(CR_{na}R_{nb})_n-$;
- 10 R_{na} and R_{nb} are each independently hydrogen or C_{1-6} alkyl;
- n is an integer from 0 to 5;
- R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;
- R^3 and R^4 each independently represent hydrogen or C_{1-6} alkyl;
- 15 R^7 represents hydrogen or C_{1-6} alkyl;
- R^8 represents hydrogen or C_{1-6} alkyl;
- and salts and solvates thereof;
- with the proviso that the following compounds are excluded;
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(pyridin-3-ylmethyl)urea;$
- 20 $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(6-methoxypyridin-3-yl)methyl]urea;$
- $5-\{[(4-(3,4-dichlorobenzyl)morpholin-2-yl)methyl]amino\}carbonyl]-amino)methyl)nicotinamide;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(1H-indol-5-ylmethyl)urea;$
- 25 $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(1H-indol-4-ylmethyl)urea;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(5-methylisoxazol-3-yl)methyl]urea;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(thien-2-ylmethyl)urea;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(2-thien-2-ylethyl)urea;$
- 30 $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(5-[(dimethylamino)methyl]-2-furyl)methyl]urea;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(3-methoxyisothiazol-5-yl)methyl]urea;$
- $N-[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-(4-methyl-1,3-thiazol-2-$

- yl)methyl]urea;
 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)urea;
 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-methyl-1,3-thiazol-4-
 -yl)methyl]urea;
- 5 methyl 2-({{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]-
 -amino}-methyl)-4-methyl-1,3-thiazole-5-carboxylate;
- N-[(5-amino-1-phenyl-1H-pyrazol-4-yl)methyl]-N'-{{4-(3,4-dichlorobenzyl)}-
 -morpholin-2-yl]methyl]urea;
- N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-pyrrolo[2,3-b]pyridin-3-
 10 -ylmethyl)urea;
- N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(5-[(dimethylamino)-
 -methyl]thien-2-yl]methyl)urea;
- N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-furylmethyl)urea;
- N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-methyl-2H-tetraazol-
 15 -5-yl)methyl]urea;
- N-{{3-(4-chlorophenyl)isoxazol-5-yl]methyl}-N'-[(2S)-4-(3,4-dichlorobenzyl)-
 -morpholin-2-yl]methyl]urea;
- N-{{(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-methyl-2H-tetraazol-
 -5-yl)methyl]urea;
- 20 N-{{(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-methyl-1,3-thiazol-2-
 -yl)methyl]urea;
- N-{{(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)}-
 -urea, and;
- N-{{(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3-(4-methoxyphenyl)-
 25 -isoxazol-5-yl)methyl]urea.

2. A compound of formula (I) according to claim 1 wherein R¹ is 3-
 formamido-1,2,4-triazol-5-yl, 5-trifluoromethyl-1,3,4-oxadiazol-2-yl, 5-(morpholin-
 4-ylmethyl)-1,3,4-oxadiazol-2-yl, 5-(N,N-diethylaminomethyl)-1,3,4-oxadiazol-2-
 30 -yl, 5-ethylaminomethyl-1,3,4-oxadiazol-2-yl, furan-2-yl, 4-(3-methyl-1,2,4-
 -oxadiazol-5-yl)furan-2-yl, 4-(3-methyl-1,2,4-triazol-5-yl)furan-2-yl, 4-(5-methyl-
 1,3,4-oxadiazol-2-yl)furan-2-yl, imidazol-2-yl, 1-methylimidazol-5-yl, imidazol-4-yl,
 3-(cyclopropylmethylaminocarbonyl)isoxazol-5-yl, 3-(N-
 pyrrolidinecarbonyl)isoxazol-5-yl, 4-methoxycarbonyloxazol-2-yl, 4-
 35 ethylaminocarbonyloxazol-2-yl, 4-cyclopropylmethylaminocarbonyloxazol-2-yl, 4-
 methylaminocarbonyloxazol-2-yl, 4-(N-pyrrolidinecarbonyl)oxazol-2-yl, 4-iso-
 propylaminocarbonyloxazol-2-yl, 1-methylcarbonylpyrazol-3-yl, pyridin-4-yl,
 pyridin-2-yl, pyridin-3-yl, 5-aminocarbonylpyridin-3-yl, 4-aminopyrimidin-5-yl, 4-
 hydroxy-2-methylpyrimidin-5-yl, 1-methyltetrazol-5-yl, 2-
 40 methoxycarbonylmethyltetrazol-5-yl, 1-methoxycarbonylmethyltetrazol-5-yl, 2-

- cyclopropylmethyltetrazol-5-yl, 1-cyclopropylmethyltetrazol-5-yl, 2-ethyltetrazol-5-yl, 1-ethyltetrazol-5-yl, 2-tert-butyltetrazol-5-yl, 5-trifluoromethyltetrazol-2-yl, 2-cyanomethyltetrazol-5-yl, 1-cyanomethyltetrazol-5-yl, 2-*iso*-butyltetrazol-5-yl, 1-*iso*-butyltetrazol-5-yl, 4-(*iso*-propylaminocarbonyl)thiophen-2-yl, 4-
- 5 (methylaminocarbonyl)thiophen-2-yl, 4-(ethylaminocarbonyl)thiophen-2-yl, 2-(*iso*-propyl)tetrazol-5-yl, 1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 3-methylaminocarbonyl-1,2,4-oxadiazol-5-yl, 3-ethylaminocarbonyl-1,2,4-oxadiazol-5-yl, 5-(5-methylisoxazol-3-yl)-1,2,4-
- 10 oxadiazol-3-yl, 5-methylaminocarbonyl-1,2,4-oxadiazol-3-yl, 2-methyl-1,3,4-oxadiazol-5-yl, pyrazin-2-yl, 3-methylisoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 3-(pyrrolidine-N-carbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 5-(ethylaminocarbonyl)-1,2,4-oxadiazol-3-yl, 3-(cyclopropylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-
- 15 propyl(methyl)aminocarbonyl)-1,2,4-oxadiazol-5-yl, 1-*iso*-propyltetrazol-5-yl, tetrazol-5-yl, 3-amino-1,2,4-triazol-5-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 2-methylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-ethylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-(*iso*-propylaminocarbonyl)-1,3,4-oxadiazol-5-yl, 2-carboxyfuran-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-
- 20 -(ethylaminocarbonyl)furan-5-yl, 2-(*iso*-propylaminocarbonyl)furan-5-yl, 1-methylpyrazol-3-yl, pyrazol-3-yl, 3-methylpyrazol-5-yl, 3-(ethoxycarbonyl)isoxazol-5-yl, 2-methyltetrazol-5-yl, 3-(methylaminocarbonyl)furan-5-yl, 3-(ethylaminocarbonyl)furan-5-yl, 3-(*iso*-propylaminocarbonyl)furan-5-yl, 3-(methylaminocarbonyl)isoxazol-5-yl, 3-
- 25 (ethylaminocarbonyl)isoxazol-5-yl, 3-(dimethylaminocarbonyl)isoxazol-5-yl, 3-(*iso*-propylaminocarbonyl)isoxazol-5-yl, 4-(methylaminocarbonyl)thiazol-2-yl, 4-(ethylaminocarbonyl)thiazol-2-yl, 4-(dimethylaminocarbonyl)thiazol-2-yl, 4-(*iso*-propylaminocarbonyl)thiazol-2-yl, 4-(ethoxycarbonyl)thiazol-2-yl, 4-carboxythiazol-2-yl, 2-(methylaminocarbonyl)thiophen-5-yl, 2-
- 30 (ethylaminocarbonyl)thiophen-5-yl, 2-(*iso*-propylaminocarbonyl)thiophen-5-yl, 2-(methylaminocarbonyl)thiophen-4-yl, 2-(ethylaminocarbonyl)thiophen-4-yl, 2-(*iso*-propylaminocarbonyl)thiophen-4-yl, 2-(methoxycarbonyl)thiophen-4-yl, 2-carboxythiophen-4-yl, 2-(methoxycarbonyl)thiophen-5-yl, 2-carboxythiophen-5-yl, 3-(ethoxycarbonyl)furan-5-yl, 3-carboxyfuran-5-yl, benzofuran-3-yl, benzimidazol-
- 35 2-yl, or 3-(1,3,4-oxadiazol-2-yl)furan-5-yl.

3. A compound of formula (I) according to claim 1 or claim 2 wherein R_{na} and R_{nb} are both hydrogen.

4. A compound of formula (I) according to any one of the preceding claims wherein n is 0, 1, or 2.
 5. A compound of formula (I) according to claim 4 wherein n is 1 or 2.
 6. A compound of formula (I) according to any one of the preceding claims wherein R³ and R⁴ are both hydrogen.
 7. A compound of formula (I) according to any one of the preceding claims 10 wherein R² is phenyl substituted with chloro or fluoro, or R² is thiophenyl substituted with chloro.
 8. A compound of formula (I) according to claim 7 wherein R² is 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chlorophenyl, 2-chlorothiophen-5-yl, or 4-fluorophenyl.
 9. A compound of formula (I) according to any one of the preceding claims wherein R⁷ is hydrogen or methyl.
-
- ~~20 10. A compound of formula (I) according to claim 9 wherein R⁷ is hydrogen.~~
11. A compound of formula (I) according to any one of the preceding claims wherein R⁸ is hydrogen or methyl.
 - 25 12. A compound of formula (I) according to claim 11 wherein R⁸ is hydrogen.
 13. A compound of formula (I) according to claim 1 selected from the Examples.
 - 30 14. A compound of formula (I) according to claim 13 selected from Examples 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 32, 33, 34, 35, 36, 38, 40, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 74, 75, 76, 77, 78, 79, 93, 95, 97, 98, 99, 101, 104, 106, 108, 109, 110, 111, 112, 113,
 - 35 114, 115, 116, 117, 118, 120, 139, 141, 142, 146, 150, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 169, 170, 171, 181, and 182.
 15. A compound of formula (I) according to claim 13 selected from Examples 1, 2, 7, 8, 9, 10, 11, 12, 16, 18, 19, 21, 24, 36, 38, 43, 44, 45, 49, 50, 55, 56, 57, 40 58, 59, 60, 61, 62, 63, 66, 67, 74, 75, 76, 77, 78, 79, 97, 99, 101, 108, 109, 110,

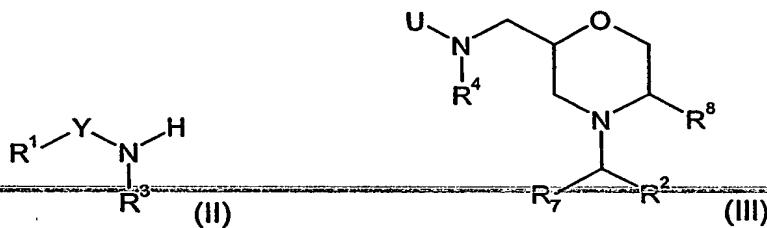
111, 112, 113, 114, 115, 116, 117, 118, 153, 154, 155, 157, 159, 160, 161, 163, 164, 169, 170, 171, and 182.

16. A compound of formula (I) according to claim 13 selected from Examples 5 2, 10, 12, 16, 19, 21, 24, 38, 50, 55, 56, 57, 60, 61, 62, 63, 74, 75, 97, 108, 110, 111, 112, 113, 114, 115, 116, 153, 155, 159, 164, 169, 170, 171, and 182.

17. A compound of formula (I) according to claim 13 selected from Examples 2, 12, 16, 19, 38, 50, 55, 56, 57, 60, 61, 74, 75, 97, 111, 113, 114, 115, 116, 159, 10 170, and 182.

18. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises the reaction of a compound of formula (II) with a compound of formula (III);

15



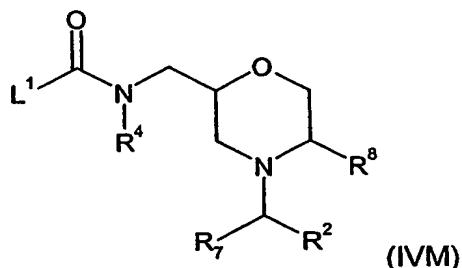
wherein;

R¹, Y, R³, R⁴, R⁷, R⁸, and R² are as hereinbefore defined for formula (I)
20 and U is a urea-forming group;
and thereafter, if required, carrying out one or more of the following optional steps:
(i) converting a compound of formula (I) to a further compound of formula (I);
(ii) removing any necessary protecting group;
25 (iii) preparing a salt or solvate of the compound so formed.

19. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein R⁷ represents hydrogen, which process comprises the reaction of a compound of formula (IV) wherein R⁷ is hydrogen with a compound of 30 formula R¹-Y-NCO wherein R¹ and Y are as hereinbefore defined and thereafter, if required, carrying out one or more of the following optional steps:
(i) converting a compound of formula (I) to a further compound of formula (I);
(ii) removing any necessary protecting group;
(iii) preparing a salt or solvate of the compound so formed.

35

20. A process for the preparation of a compound of formula (I) as defined in claim 1 which process comprises the reaction of a compound of formula (IVM)



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wherein R², R⁴, R⁷, and R⁸ are as hereinbefore defined and L¹ is a resin-bound leaving group, for example a polystyrene resin-bound, typically a Merrifield resin-bound, 4-thiophenoxy group, with a compound of formula (II) and thereafter, if required, carrying out one or more of the following optional steps:

- 10 (i) converting a compound of formula (I) to a further compound of formula (I);
 (ii) removing any necessary protecting group;
 (iii) preparing a salt or solvate of the compound so formed.

21. A compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

22. A compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

20

23. Use of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

25 24. A method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof.

30 25. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

26. A compound selected from the list consisting of:

- [(2S)-4-(3-Chloro-4-fluoro-benzyl)morpholin-2-ylmethyl]carbamic acid tert-butyl ester;
- C-[(2S)-4-(3-Chloro-4-fluoro-benzyl)-morpholin-2-yl]-methylamine;
- [(2S)-4-(3-Chloro-4-fluoro-benzyl)morpholin-2-ylmethyl]carbamic acid 4-nitro-
5 phenyl ester;
- 1-(5-Chloromethyl-[1,3,4]oxadiazol-2-ylmethyl)-3-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-ylmethyl]urea;
- {(2S)-4-[1-(3,4-Difluorophenyl)ethyl]morpholin-2-ylmethyl}carbamic acid 4-nitro-phenyl ester;
- 10 {(2S)-4-[1-(3,4-Difluorophenyl)ethyl]morpholin-2-ylmethyl}carbamic acid 4-nitro-phenyl ester Isomer I;
- {(2S)-4-[1-(3,4-Difluorophenyl)ethyl]morpholin-2-ylmethyl}carbamic acid 4-nitro-phenyl ester Isomer II;
- C-[(2S)-4-[1-(3,4-Difluorophenyl)ethyl]morpholin-2-yl]methylamine
- 15 dihydrochloride;
- {(2S)-4-[1-(3,4-Difluoro-phenyl)-ethyl]-morpholin-2-ylmethyl}-carbamic acid tert-butyl ester;
- N'-(5-{3-[(2S)-4-(3,4-Dichloro-benzyl)morpholin-2-ylmethyl]ureidomethyl}furan-3-carbonyl)hydrazinecarboxylic acid tert-butyl ester;
- 20 1-[(2S)-4-(3,4-Dichloro-benzyl)morpholin-2-ylmethyl]-3-(4-hydrazinocarbonyl-furan-2-ylmethyl)urea hydrochloride, and;
- 1-[4-(N'-Formyl-hydrazinocarbonyl)furan-2-ylmethyl]-3-[(2S)-4-(3,4-dichloro-benzyl)morpholin-2-ylmethyl]urea.
- 25 27. A compound selected from the list consisting of:
- 2-(5-Methyl-[1,3,4]oxadiazol-2-yl)ethylamine hydrochloride;
- 5-Aminomethyl-[1,3,4]oxadiazole-2-carboxylic acid methylamide hydrochloride;
- 2-Aminomethyloxazole-4-carboxylic acid methyl ester;
- 5-[(2,2,2-Trifluoro-acetylamino)methyl]furan-3-carboxylic acid methylamide;
- 30 5-Aminomethyl-furan-3-carboxylic acid methylamide;
- [3-(N'-Acetyl-hydrazino)-3-oxo-propyl]carbamic acid tert-butyl ester;
- [2-(5-Methyl-[1,3,4]oxadiazol-2-yl)ethyl]carbamic acid tert-butyl ester;
- 5-Aminomethylthiophene-3-carboxylic acid methylamide;
- 5-[(2,2,2-Trifluoroacetylamino)methyl]thiophene-3-carboxylic acid methylamide,
- 35 and;
- (5-Methylcarbamoyl-[1,3,4]oxadiazol-2-ylmethyl)carbamic acid tert-butyl ester.